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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/701,618	ROTHBARTH ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7 and 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 December 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The communication filed 11/16/04 is acknowledged. The amendment has been entered. Claims 1-4, 7 and 8 are currently pending in the application and are addressed herein.

Election/Restrictions

Applicant's election of Group I in the reply filed on 11/16/04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

It is noted that claims 5 and 6, drawn to a non-elected invention, have been cancelled.

Claims 1-4, 7 and 8 are examined herein.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 4/2/02 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification/Sequence Rules

The specification is objected to for the following reasons:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 because (for example) pages 9 and 11 of the specification comprise disclosure of nucleotide

sequences which require sequence identifiers (SEQ ID NO), but no SEQ ID NO has been assigned to the sequences. It is noted that the Paper sequence listing discloses several oligonucleotide sequences (e.g., see SEQ ID NOS: 5-10). It appears that the improper sequences (e.g., see pages 9 and 11) merely need to be assigned the appropriate SEQ ID NOS., as indicated in the Paper sequence listing. However, should the sequences disclosed in the specification not be present in the paper sequence listing, a new paper listing and CRF containing the sequences and assigning an appropriate SEQ ID NO must be submitted.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps which are taken to cause the overexpression of the C1D gene.

The claims are drawn to a method of inducing apoptosis in cells by overexpression of the C1D gene. However, there are no steps claimed which indicate what action is taken to cause the overexpression of the C1D gene. It is noted that claim 4, 7 and 8 indicate that an expression vector comprising the C1D gene is delivered to cells, which is considered an example of an essential method step. Amending the instant claims to indicate that the cells are transfected with an expression vector comprising SEQ ID NO: 1 or SEQ ID NO: 3, would obviate this rejection.

Claims 1 and 3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites the limitation "the C1D gene product" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. It is noted that claim 1 recites the phrase "the C1D gene" which is a nucleic acid sequence, while claim 3 recites the phrase "the C1D gene product comprising the amino acid sequence of..." which is clearly an amino acid sequence. Therefore, there is insufficient antecedent basis for this limitation in the claim. It is noted that amending claim 3 to recite "wherein the C1D gene encodes the amino acid sequence of..." instead of "the C1D gene product comprising the amino acid sequence of..." would obviate this rejection.

Additionally, claim 3 recites that phrase "the DNA sequence of the later amino acid sequence hybridizing with the DNA of ...". This phrase renders the claim indefinite as it is unclear what "the DNA of the second amino acid sequence" actually is because DNA sequences are not "of" amino acid sequences; rather DNA sequences encode amino acid sequences. Furthermore, term "hybridizing" renders the claim indefinite as it is unclear what is "hybridizing", (e.g., the DNA or the second amino acid sequence).

Claim 1 must encompass all of the limitations (including the indefinite limitations) of the dependent claim because is the base claim from which claim 3 depends. Therefore, claim 1 is rejected for the same reasons.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a method of inducing apoptosis in cells by overexpression of the C1D. As indicated above, the broad claim is not limited to any particular method. Therefore, the claims encompass any methods which result in the overexpression of the C1D gene, including administering agents such as small molecules, polypeptides, nucleic acids, etc.

Additionally, dependent claims indicate that the claims encompass transfecting the cells with an expression vector comprising: (a) a DNA encoding SEQ ID NO: 1, SEQ ID NO: 3 or a DNA differing by one or several base pairs wherein the differing DNA is capable of hybridizing with SEQ ID NO: 1 or SEQ ID NO: 3; or (b) a DNA related to the DNA from (a) via the degenerate genetic code.

Therefore, the instant claims encompass a genus of molecules which can comprise a huge number of vastly different molecules including molecules that are not structurally related and which have different functions (such as small organic molecules, nucleic acids sequences and

amino acid sequences) including molecules which have yet to be identified. Furthermore with respect to genus of nucleic acids, the claims encompass nucleic acids which differ by several base pairs with the only limitation that the nucleic acid can hybridize to SEQ ID NO: 1 or 3. It is noted that there is no indication that the nucleic acid sequence encodes a polypeptide with a particular function. Therefore, the nucleic acids encompassed by the claims includes nucleic acids that hybridize to SEQ ID NO: 1 or 3, but which encode polypeptides that have different functions than the polypeptides encoded by SEQ ID NO: 1 and 3.

Therefore, the instant claims encompass a genus of molecules that includes a vast number of different species molecules wherein the species can have different structures and functions including molecules which have yet to be identified.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a nucleic acid encoding SEQ ID NO: 2 or SEQ ID NO: 4. The specification does not identify any particular structure-function relationship for the claimed genus of molecules. Furthermore, with respect to the genus of nucleic acids encompassed by the claims, there is no disclosure of any common sequence structures which are critical to the function of the claimed genus of nucleic acids. Furthermore, the prior art does not disclose any molecules which cause the overexpression of C1D in a cell resulting in apoptosis in the cell. Accordingly, in the absence of

sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of molecules, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

The only specific molecules disclosed in the specification which can cause overexpression of C1D in a cell and result in the induction of apoptosis in the cell is an expression vector comprising a nucleic acid sequence encoding either SEQ ID NO: 2 or SEQ ID

NO: 4. Therefore, there is insufficient written description of the broad genus of molecules encompassed by the claims.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-4, 7 and 8 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> A method for inducing apoptosis in tumor cells wherein said method comprises administering directly to the tumors cells an expression vector encoding SEQ ID NO: 2 or SEQ ID NO: 4 whereby SEQ ID NO: 2 or SEQ ID NO: 4 is overexpressed in the tumor cells in an amount effective for inducing apoptosis in said tumor cells.

does not reasonably provide enablement for the full scope encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

> *Wands* states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a method for inducing apoptosis in cells. The specification indicates that the cells can be tumor cells wherein the tumor cells are in vivo. Therefore, the nature of the invention is gene therapy

The breadth of the claims

The claims are very broad and encompass a method for inducing apoptosis in cells by overexpressing C1D in the cells. The method encompasses inducing C1D overexpression by administering an agent such as an expression vector encoding a fragment or variant of SEQ ID NO: 2 or 4 (including fragments and variants which do not have the same function as SEQ ID NO: 2 or 4). Furthermore, the specification discloses that the target cells can be tumor cells and the tumor cells can be in vivo (in a subject). Therefore, the claims encompass inducing apoptosis in a tumor in a subject by administering an agent, such as an expression vector (as indicated above) wherein the agent is administered by any route of administration.

The unpredictability of the art and the state of the prior art

With respect to the induction of apoptosis of cells in vivo (e.g., gene therapy), it is noted that the prior art teaches that there are a number of significant obstacles which must be overcome before gene therapy can be considered a routine science.

Specifically, **Anderson (Nature 1998; 392:25-30)** teaches "... there is still no conclusive evidence that gene-therapy protocol has been successful in the treatment of a human disease." (see p. 25). Furthermore, **Check (Nature 2003; 421: 678)** teaches that the nucleic acids encoding the therapeutic products may be erroneously inserted into a critical element, thus disrupting a particular gene resulting in unknown, adverse or detrimental effects. Specifically,

Check teaches the occurrence of leukemia due to insertion nucleic acids used in gene therapy into a particular stretch of DNA. (See p. 678).

Furthermore it is well established in the art that delivery is one of the key problems of gene therapy. Regarding delivery in general, **Anderson (Nature 1998; 392(suppl):25-30)** teaches,

> "The challenge is to develop gene therapy as an efficient and safe drug delivery system. The goal is more difficult to achieve than many investigators had predicted... The human body has spent many thousands of years learning to protect itself from the onslaught of environmental hazards, including the incorporation of foreign DNA into its genome. (See p. 25, second paragraph). The ultimate goal of gene therapy research is the development of vectors that can be injected, will target specific cells, will result in safe and efficient gene transfer into a high percentage of those cells, will insert themselves into appropriate regions of the genome (or will persist as stable episomes), will be regulated be either by administered agents or by the body's own physiological signals, will be cost effective and will cure disease." (See p. 30, first paragraph).

Crystal (Science 1995; 270:404-410) also indicates some of the problems regarding delivery. Specifically, regarding the obstacles of human gene transfer, Crystal teaches, "The [gene transfer] vector (should) be specific for its target, not recognized by the immune system..." (See p. 409, column 2 under "The perfect vector").

Finally, regarding the delivery of gene therapy vectors to tumors, but applicable to the specific delivery of all gene therapy molecules, **Greco (Frontiers in Biosci. 2002; 7:d1516-1524)** teaches,

> The administration of gene therapy vectors requires that they be not only targeted, but also protected from degradation, sequestration or immune attack, in order to reach the appropriate sites for transfection. Although some success has been reported for naked DNA, efficient delivery has been restricted to intratumoral injection. (See p. 1517, paragraph bridging columns 1-2).

Therefore, it is clear that the prior art indicates that direct delivery of the therapeutic nucleic acid to the desired site of transfection (i.e., directly to the target cells) is critical for delivering the nucleic acid to the appropriate cells.

There is no indication in the prior art or the specification that C1D overexpression can induce apoptosis in any type of cell other than a tumor cell.

Working Examples and Guidance in the Specification

The specification discloses by example that administration of expression vectors directly to tumor cells in vitro. The expression vectors used in the examples encoded either SEQ ID NO: 2 or SEQ ID NO: 4. There are examples in the specification indicating that any other agent can induce C1D overexpression and apoptosis in a cell. There are no examples indicating that any fragments or variants of SEQ ID NO: 2 or 4 can effectively induce apoptosis in a cell. Furthermore, there are no examples indicating that the disclosed expression vectors can induce apoptosis in any cell other than a tumor cell.

Quantity of Experimentation

Considering the breadth of the claims, an enormous amount of experimentation would have to be performed in order for one of skill in the art to be able to practice the claimed invention to the full scope encompassed by the claims. For instance, additional experimentation would be required with respect to the therapeutic compounds encompassed by the claims not adequately described in the specification. Further experimentation would be required to overcome the art-recognized problems associated with delivery of gene therapy vectors for treating tumors in a subject. And finally, additional experimentation would be

required in order to show that the methods could be used to induce apoptosis in non-tumor cells.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the nature of the invention, the breadth of the claims, the unpredictable nature of the invention as recognized in the prior art, the limited amount of working examples and guidance provided, and the high degree of skill required to practice the invention, it is concluded that the specification does not provide an enabling disclosure for the full breadth of the instant claims. Therefore, additional experimentation is required before one of skill in the art could make and use the claimed invention. The amount of additional experimentation required to perform the broadly claimed invention is undue.

It is noted that amending the claims as indicated above (see scope of enablement) would obviate the instant rejections.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon Eric Angell
Art unit 1635

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PRIMARY EXAMINER